Cost-effectiveness and budget impact of docetaxel, abiraterone, enzalutamide, apalutamide or radiotherapy plus androgen deprivation therapy versus androgen deprivation therapy alone in newly diagnosed metastatic hormone-sensitive prostate cancer

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Cost-Effectiveness and Budget Impact of Docetaxel, Abiraterone, Enzalutamide, Apalutamide or Radiotherapy plus Androgen Deprivation Therapy versus Androgen Deprivation Therapy Alone in Newly Diagnosed Metastatic Hormone-Sensitive Prostate Cancer

Health Economic Analysis Plan

Swiss Medical Board Health Technology Assessment

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Background and rationale

Prostate cancer is the most frequent cancer in men, placing a high burden on patients and healthcare systems. With an age-standardized incidence of 115.7/100,000 person-years, prostate cancer is currently estimated to affect over 43,000 patients in Switzerland [1]. Prostate cancer is characterized by a relatively slow disease progression, especially when detected and treated in early, localized stages. This manifests in a relatively high 5-year survival of 88.6% after diagnosis, while the mortality rate of 22.0/100,000 person-years is still high compared to other cancer types [1]. Prostate cancer and its progression typically are androgen-dependent and respond well to treatments that reduce the production of androgens including testosterone. Androgen deprivation therapy (ADT) is the standard of care for men with metastatic, hormone-sensitive prostate cancer (mHSPC), either by means of surgical castration (orchiectomy) or medical castration [2]. These treatments constitute the mainstay of therapy for prostate cancer patients in high-risk localized as well as advanced (i.e., locally progressive or metastatic) disease stages. In recent years, substantial advances have been made in the treatment of prostate cancer, significantly improving the prognosis of patients with advanced disease.

A subject of high current scientific interest is the management of patients with newly diagnosed mHSPC [3–5]. Patients are typically diagnosed with mHSPC either as their first diagnosis of prostate cancer, or in the context of progression from localized to metastatic disease. Patients are defined as having "hormone-sensitive" disease if they have either not previously received ADT or have demonstrated ongoing sensitivity to ADT. Several different treatments are now available that have shown benefits in mHSPC patients in combination with ADT. These treatments include chemotherapy with docetaxel, novel hormonal treatments (i.e., second-generation anti-androgens) such as abiraterone, enzalutamide and apalutamide, as well as radiotherapy. Both docetaxel and abiraterone demonstrated significant effects in prolonging overall survival [6–13]. Enzalutamide and apalutamide showed promising results on overall survival in early analyses [14–16]. These effects may, however, depend on the volume and risk category of the disease, as well as on whether mHSPC was diagnosed *de novo* (i.e., as the first diagnosis) or after prior local therapy (i.e., local treatment of the primary tumor). Additionally, external beam radiotherapy to the prostate has been shown to have survival benefits in the subgroup of prostate cancer patients with low disease volume, but not in the overall mHSPC population [17,18]. The optimal treatment for men with newly diagnosed mHSPC is thus currently unclear and additionally depends on clinical factors and patient preferences.

Only treatment with abiraterone (limited to high risk mHSPC) has received marketing approval for mHSPC by swissmedic, and is regularly reimbursed by the Swiss statutory health insurance [19,20]. Docetaxel is commonly used *off-label* in this indication. Docetaxel is available as a generic drug in

Switzerland [19], while a current legal dispute over the patent on abiraterone in the United States may open the market for generic versions of this drug before formal patent expiration [21]. According to Swiss experts, local radiotherapy primarily performed in men with newly diagnosed mHSPC with low disease volume or low risk and a good overall health state. Currently, radiotherapy is rather seen as a supplement to systemic therapies in Switzerland. This is also reflected in current clinical practice guidelines [22].

Aim of this HTA

The aim of the economic part of this Health Technology Assessment (HTA) is to assess and evaluate the cost-effectiveness and budget impact of the different available systemic first-line treatments for adult men with newly diagnosed mHSPC.

PICO

This chapter describes the PICOs (Population, Intervention, Comparator, Outcomes) of the economical part but also the clinical parameters used as input into the health economic analysis.

Population

The primary target population of this HTA are adult men with mHSPC that have not previously undergone systemic therapy. Study participants will be considered eligible if they have not previously received ADT, have received ADT but more than 12 months prior to enrollment for a total duration of less than 24 months, or have received ADT but for less than 6 months prior to enrollment and without clinical, biochemical or radiographical indication of disease progression. We will exclude patients with non-metastatic (M0) prostate cancer, as well as patients that have received chemotherapy or newer-generation hormonal therapy prior to enrollment.

In case we identify studies from which only a subpopulation of participants fulfills the eligibility criteria, we will include the study and use corresponding subgroup data in our analysis if the main outcomes necessary for the health economic analysis are available. If no stratified data are available, we will use data from the overall study population or a subpopulation which we judge to be most applicable, if at least 80% of participants are eligible or if there is sufficient evidence to assume an absence of effect modification across the corresponding strata. Else, we will exclude the study from the primary analysis and conduct sensitivity analyses including data from these studies.

We define metastatic cancer as the presence of one or more distant metastases irrespective of the extension of the primary tumor and lymphatic spread (i.e., M1 stage with any T and N stage according to the TNM classification). The term "hormone-sensitive" will be considered synonymous to the terms "castration-sensitive", "hormone-naïve" and "castration-naïve" prostate cancer. This includes clinical scenarios in which patients have either not previously received ADT or have demonstrated ongoing sensitivity to ADT [3]. Studies including more than 10% of patients with rare forms of prostate cancer, such as aggressive variant prostate cancer (i.e., with neuroendocrine differentiation or small cell features) are excluded. Patients with non-metastatic (M0) prostate cancer are excluded, but may be considered in secondary analyses or if data availability dictates so.

Intervention

The following interventions will be considered eligible:

- ADT + docetaxel, intravenous chemotherapy (in combination with prednisone) followed by ADT alone
- ADT + abiraterone (in combination with prednisone), daily oral medication
- ADT + enzalutamide, daily oral medication
- ADT + apalutamide, daily oral medication
- ADT + radiotherapy, external beam radiation therapy to the prostate followed by ADT alone (for a potential subgroup analysis of *de novo* low risk patients)

Any concurrent or protocolized immediate sequential combination of the aforementioned treatments will also be included.

Excluded interventions are:

- Bone agents (such as zoledronic acid)
- COX-2 inhibitors (such as celecoxib)

Comparator

The aforementioned experimental interventions will be compared between each other and against the following comparator intervention:

- ADT alone or in combination with first-generation non-steroidal anti-androgens.

ADT may involve treatment with gonadotropin-releasing hormone agonists or antagonists, or bilateral orchidectomy, alone or in combination with first-generation non-steroidal anti-androgens (such as bicalutamide, flutamide or nilutamide).

Clinical parameters

The following outcome parameters of the clinical systematic review are considered as inputs for the health economic analysis:

- Overall survival (OS)
- Progression-free survival (PFS) (expressed by one of the following outcomes, whichever is judged to most closely reflect a meaningful clinical progression in the following order of priority):
  - Clinical PFS (cPFS) defined as the time from randomization to first clinical or radiographic progression, or death.
  - Radiographic PFS (rPFS) defined as the time from randomization to first radiographic progression, or death.
  - Failure-free survival (FFS): Defined as the time from randomization to first clinical, radiographic or biochemical (prostate-specific antigen, PSA) progression, or death.
- Biochemical (PSA) PFS (bPFS): Defined as the time from randomization to first biochemical (PSA) progression, or death. Overall health-related quality of life (QoL) (e.g. measured by the EQ-5D instrument)
- Grade 3-4 adverse events (AEs)

Health Economic outcomes

- Relevant resource use parameters (including among others: doses of medications, frequency and type of drug administration, frequency and extent of physician visits, frequency and type of imaging, resource use due to AEs)
- Direct costs related to resource use utilization (drug cost for first-line and further-line concomitant medication, administration costs, physician visit costs, imaging costs, AE costs)
- Quality-adjusted life years (QALY) gained, life-years (LY) gained
- Incremental cost-effectiveness ratio (ICER; costs per QALY or LY gained)
- Budget impact estimates (estimated number of cases per year and related costs)

Health economic systematic literature review

A systematic review of the current health economic literature is currently being undertaken. Literature on the cost-effectiveness of abiraterone, enzalutamide, apalutamide, docetaxel, and radiotherapy in patients with mHSPC is identified. The identified economic studies will be critically assessed according

to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist [23]. Plausibility of the results and the transferability of international results to Switzerland will be considered.
Main results will be summarized in tabular and/or graphical formats and synthesized narratively.

Cost-effectiveness analysis

Model structure and development

A *de novo* cost-effectiveness analysis will be conducted for Switzerland including all treatments listed in the PICO, with the exception of local radiotherapy. An additional analysis of the subgroup of *de novo* low-risk patients comparing ADT monotherapy to ADT+radiotherapy might be envisaged. A three-health state Markov (M) model with the states of progression-free survival (PFS), progressive disease (PD) and death (D) will be developed. We will choose a model cycle length of 1 month applying half-cycle correction. We further assume that a very large percentage of the patients (90-95%) receives second and further lines of treatment within a 15-year time horizon. Due to the complexity and diversity of the possible follow-up treatments, a possible lack of information, and their dependence on first-line treatment, we may combine post-progression treatments in one "progressive disease" health state.
The original Kaplan-Meier (KM) OS and PFS curves from relevant studies (consistent with the clinical part of this HTA) will be digitalized (Software DigitizeIt). For this purpose, individual patient data (IPD) and Kaplan-Meier estimates will be re-created following the approach of Guyot et al. [24]. The proportional hazard (PH) assumption will be verified based on the Schoenfeld test and/or based on visual inspection [25]. In case it is not substantially violated, frailty models or mixed effects Cox models will be used to perform a meta-analysis of the various ADT time-to-event curves. Survival curves of the intervention arms will be obtained by applying hazard ratios to the ADT baseline hazard. We intend to perform long-term data extrapolation by fitting different parametric distributions to the pooled ADT data. Survival curves with the best fit, based on the Akaike and Bayesian information criterion (AIC and BIC) as well as based on clinical plausibility of long-term model extrapolations will be selected for the time periods after the study have ended, and combined with general population mortality in Switzerland. In case the PH assumption is substantially violated, other methods like e.g. flexible parametric models or piecewise exponential models will be explored [26,27].
If intermediate results generated during the research process lead to modifications of the described approach, this will be transparently reported.

Perspectives

The cost-effectiveness analysis will be performed from a 'KVG perspective' (considering the direct medical costs of all health care services covered by the Swiss statutory health insurance, irrespective of the actual payer).

Time horizon

The time horizon for the cost-effectiveness analysis needs to be long enough to capture the clinical and economic differences arising from the different treatment options. All treatments of interest are relatively new, and the longest-follow period available from an original study is 9 years. Hence, long-term extrapolation underlies very substantial uncertainty. As a compromise, we plan a time horizon of 15 years in a base case analysis. A lifelong time horizon (30 years), conceptually the most appropriate, may be envisaged in a scenario analysis implying a need for a longer and more uncertain extrapolation.

Discounting

Costs and utilities will be discounted at an annual rate of 3.0%.

Uncertainty

In order to investigate parameter and structural uncertainty, we will perform one-way and probabilistic sensitivity analyses, and several scenario analyses.

For the probabilistic sensitivity analyses, we plan to assign gamma distributions to unit cost parameters, beta distributions to utilities and probabilities. Parameter estimates of the OS and PFS curves will be assigned normal distributions, and hazard ratios log-normal distributions. Distribution parameters considering available standard errors will be used for the probabilistic sensitivity analyses with 10,000 simulation runs. Where standard error estimates or 95% confidence intervals (CIs) are not available, we will assume standard errors to be 20% of the base case parameter values (10% for utilities). For the univariate sensitivity analyses, available 95% CIs will be used as the maximum and minimum boundaries. Otherwise, we plan to vary the base case parameters by ±30%.

The selection of scenario analyses to be performed will depend on intermediate results.

Budget Impact Analyses

Budget impact analyses will be performed to compare the overall costs of ADP therapy alone with scenarios including ADT + docetaxel, ADT + abiraterone, ADT + enzalutamide, ADT + apalutamide in Switzerland assuming different market shares.

The analysis will consist of two main steps: first, the annual number of patients with mHSPC will be estimated; second, based on the annual number of cases and the costs estimated in the cost-effectiveness analysis, the total annual costs will be estimated.

Since patients are typically diagnosed with mHSPC either as their first diagnosis of prostate cancer or in the context of progression from localized to metastatic disease, the estimation of the annual number of potentially eligible cases will consist in a combination of incident and prevalent prostate cancer cases.

Data from NICER will provide an estimate of the yearly total number of new prostate cancer cases diagnosed (incident cases) as well as the total number of prostate cancer patients (prevalent cases) in Switzerland.

- Incident cases: it will be assumed that all newly diagnosed prostate cancers are hormone sensitive. To estimate which percentage of these patients may have a metastatic condition, we will apply national or published estimations. For example, in a report recently published by the German Institute for Quality and Efficiency in Health Care (IQWiG), the percentage of metastases among newly diagnosed prostate cancers ranged from 5.57% to 7% [28]. A systematic review and meta-analysis investigating the diagnostic performance of magnetic resonance imaging for the detection of bone metastasis in prostate cancer reported that the percentage of metastasis in four studies including newly diagnosed prostate cancer patients only ranged from 6.8% to 25.0% [29]. In the base case scenario we may assume that 10% of the newly diagnosed patients have mHSPC, whereas in the sensitivity analysis we will vary the assumed percentage (e.g. from 5% to 20%).
- Prevalent cases: published literature will be screened to investigate which percentage of the already known prostate cancer patients progress to mHPSC.

In the second step the estimated number of cases will be combined with undiscounted costs derived from the cost-effectiveness model. The budget impact will be estimated over a period of several years (e.g. from 2020 to 2025). The cost calculations will take into consideration initial treatment costs (i.e. costs in the first treatment year) as well as follow-up costs (costs in the following years). This means that every year we will sum the costs of newly diagnosed and treated mHSPC patients (first-year

treatment) with follow-up treatments of already known mHSPC cases (second/third/etc. treatment year).

The total costs will be calculated assuming that all patients receive the same therapy as well as assuming different market shares (e.g. 20% ADT + docetaxel, 40% ADT + abiraterone, 40% ADT + enzalutamide).

Several sensitivity and scenarios analyses will be performed to investigate how higher/lower prevalence and costs of mHSPC may influence the total costs.

Sources for resource use and costs

We plan to obtain information required for the economic analysis through

- The results of the clinical part of the assessment
- The results of the systematic health economic literature review
- Input from Swiss clinical experts in mHSPC
- The Swiss specialty list for drug prices (www.spezialitätenliste.ch)
- Swiss Hospital Statistics 2018: patients with prostate cancer will be identified through relevant treatments (e.g. CHOP codes), diagnostic codes (i.e. ICD-10 codes), and hospitalization codes (i.e., SwissDRG codes)
- Diagnosis Related Group case weights (SwissDRG online definition handbook 8.0 or a newer available version) for inpatient hospital costs
- Swiss tariff framework for ambulatory and outpatient care (TARMED online Browser Version 1.09 or newer)
- Swiss BAG “Analysenliste” for laboratory costs
- Additional targeted searches, complemented with hand-searches of the grey literature and the world wide web (non-systematic) in order to identify manuscripts for event rates, health resource use and costs that were not available from the above-mentioned sources

Further sources may be identified and added at a later point in time.

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